MAJOR ARTICLE

Serious Adverse Events among Participants in the Centers for Disease Control and Prevention's Anthrax Vaccine and Antimicrobial Availability Program for Persons at Risk for Bioterrorism-Related Inhalational Anthrax

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On 20 December 2001, the Centers for Disease Control and Prevention (CDC) initiated the Anthrax Vaccine and Antibiotic Availability Program (hereafter, the "Program") under an investigational new drug application with the US Food and Drug Administration. This Program provided options for additional preventive treatment for persons at risk for inhalation anthrax as a result of recent bioterrorism attacks who had concluded or were concluding a 60-day course of antimicrobial prophylaxis. Participants were offered an additional 40 days of antibiotic therapy (with ciprofloxacin, doxycycline, or amoxicillin) or antibiotic therapy plus 3 doses of anthrax vaccine. By 11 February 2002, a total of 5420 persons had received standardized education about the Program and 1727 persons (32%) had enrolled. Twelve participants have been identified as having serious adverse events (SAEs). One SAE, which occurred in a participant with ciprofloxacin-induced allergic interstitial nephritis, was considered to be probably associated with treatment received in the Program. No SAEs were associated with anthrax vaccine. CDC will continue to monitor Program participants during the next 2 years.

On 4 October 2001, the first case of inhalational anthrax in the United States in >25 years was confirmed, marking the beginning of the first outbreak of bioterrorism-related anthrax in the United States. This bioterrorist attack, which involved the use of *Bacillus anthracis,* resulted in 11 documented cases of cutaneous anthrax and 11 documented cases of inhalational anthrax, including 5 fatal cases [1]. Once the risk for inhalational anthrax was identified, recommendations were made to begin antimicrobial prophylaxis for groups who met specific exposure criteria [2]. In November 2001, in response to this attack, the Centers for Disease Control and Prevention's (CDC; Atlanta, GA) Advisory Committee on Immunization Practices (ACIP) clarified an earlier recommendation and recommended that, in the absence of available vaccine, persons potentially exposed to *B. anthracis* aerosols should receive a 60-day course of antibiotic therapy [3].

Before the start of this bioterrorist attack, both of the major US advisory bodies, the Working Group on Civilian Biodefense [4] and the ACIP [5], both of which had recently considered the issue of postexposure prophylaxis for prevention of inhalational anthrax, had rec-

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ommended the use of antibiotics in combination with Anthrax Vaccine Adsorbed (AVA; Bioport), if available. In December 2001, the US Department of Defense released AVA for immediate purchase by the US Department of Health and Human Services (DHHS) for the Anthrax Vaccine and Antibiotic Availability program (hereafter referred to as "the Program"). The CDC made the Program available on the basis of several additional considerations. First, data suggest that the spore form of the organism, which is unaffected by antibiotic therapy, may persist for >60 days before germinating and causing inhalational anthrax [6, 7]; this may be a greater concern among persons with high-level exposure. A recent simulation study in Canada indicated a higher-than-expected potential for dissemination of a large number of spores on the basis of the passive opening of a contaminated envelope [8]. Second, problems with adherence to antibiotic therapy were documented among those for whom 60 days of antibiotic prophylaxis was initially recommended [9, 10], which potentially decreased the effectiveness of such therapy. Finally, the objective of the CDC and the DHHS is to use all available means to reduce the risk of disease for exposed individuals.

Thus, in October 2001, the CDC filed an investigational new drug application with the US Food and Drug Administration (FDA) to allow for off-label use of antibiotics, as well as AVA, should it become available. On 20 December 2001, the Program was initiated to provide options for additional preventive treatment of persons who had potential significant exposure to *B. anthracis* and for whom 60 days of antibiotic prophylaxis was recommended [11]. Participants who enrolled in the Program were given a choice between 2 options intended to provide protection against the possibility that *B. anthracis* spores might cause illness up to 100 days after exposure: (1) 40 additional days of antimicrobial prophylaxis (with ciprofloxacin, doxycycline, or amoxicillin), or (2) 40 additional days of antimicrobial prophylaxis plus 3 doses of AVA administered at 2-week intervals during a 4-week period (i.e., during visits on weeks 0, 2, and 4 of the Program).

The Program enrolled persons who were exposed at affected US Postal Service facilities, affected government offices and mail facilities, and other affected business locations in 6 states and Washington, D.C. In some cases, exposed persons required transitional antibiotic treatment, ranging from 1 to 16 days in duration, until education regarding Program options could be provided and Program enrollment procedures could be implemented. Because participants were required to sign an informed consent document at enrollment, it was important to allow for an adequate opportunity for education about Program treatment options. The protocol for this Program was reviewed and approved by an institutional review board at the CDC.

METHODS

Surveillance for adverse events (AEs). Safety monitoring of Program participants occurred via both passive and active surveillance activities. Passive surveillance for AEs was conducted via the CDC "alertline" (a CDC-sponsored, 24-h, 7-days-per-week hotline established for Program participants). Participants were provided a card with the alertline number at enrollment and were encouraged to report any suspected AEs to the alertline at any time and at each clinic visit. Participants were also asked to provide information about local and systemic AEs that occurred during the 6-week period after enrollment, using diaries provided to them at enrollment. In addition, all participants were advised to report AEs to the Vaccine Adverse Event Reporting System (VAERS) and/or MedWatch system—both of which are passive surveillance systems—after vaccination or use of antibiotics. An alternative passive surveillance method used by participants was direct contact with the CDC via mail and/or telephone contact other than the CDC alertline number. Active surveillance was conducted by interviewing all participants during each of 3 scheduled clinic visits (during enrollment and 2-week and 4-week follow-up visits) about any suspected AEs. Additional active surveillance was conducted through a telephone survey performed 2 months after enrollment to solicit responses to a series of health status and safety-related questions. Additional telephone surveys are planned for 6, 12, and 24 months after enrollment.

Case definitions. According to FDA reporting requirements, an AE is defined as any untoward medical occurrence in a participant who was administered an investigational drug, including vaccine, which may have but did not necessarily have a causal relationship to the treatment. An AE, therefore, can be any unfavorable and unintended sign (including laboratory findings), symptom, or disease temporally associated with the use of the investigational therapy (e.g., a specific lot of AVA), whether or not the AE was casually associated with the study therapy [12]. A serious AE (SAE) was defined as any untoward medical occurrence that may have resulted in any of the following outcomes: (1) death, (2) life-threatening event, (3) inpatient hospitalization or prolongation of an existing hospitalization, (4) persistent or significant disability or incapacity, and/or (5) congenital anomaly or birth defect. In addition, important medical events that did not result in death, were not life threatening, or did not require hospitalization were considered SAEs when, on the basis of appropriate medical judgment, it was determined that they had the potential to jeopardize the participant's health and might have required medical or surgical intervention to prevent one of the outcomes listed above [12].

Case attribution. All AE reports received at the CDC through both active and passive surveillance were screened for

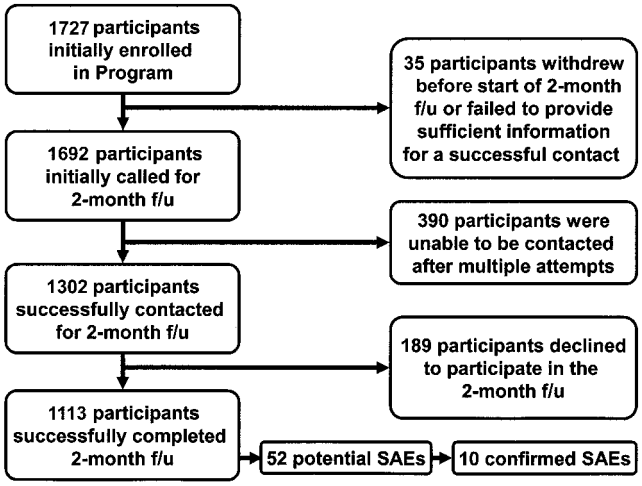


Figure 1. Distribution of Anthrax Vaccine and Antibiotic Availability Program participants at the 2-month follow-up (f/u), February–May 2002. SAE, serious adverse event.

potential SAEs. The screening was conducted by the clinical program manager or a member of his staff. A broad interpretation of the case definition of an SAE was used to determine whether the report indicated a potential SAE and thereby warranted further follow-up. As part of our conservative interpretation of persistent or significant disability, all participants who reported missing $\geqslant$2 weeks of work were evaluated as having possibly experienced an SAE, and a determination of the cause of the absence was made. If further follow-up was warranted, a member of the clinical program manager's staff attempted to contact the participant to gather additional information about the reported AE, to determine adherence of the participant to the prescribed treatment, and to request contact information for the participant's health care provider(s). Once adequate information was obtained about the AE, the clinical program manager and his staff made a determination of whether the case met the FDA definition of an SAE. The medical monitor was selected before the Program's initiation and was notified of all SAEs by the CDC. He served as an independent medical consultant who was available to the study staff during the entire Program. AE reports that proved difficult to classify as either serious or nonserious were forwarded to the medical monitor for consultation. The medical monitor's responsibilities also included determining the causal relationship between SAEs and the treatment received in the Program. SAEs were classified into the following 6 categories: "unclassifiable," "not related," "unlikely," "possible," "probable," and "definite." Case summaries of all SAEs were then forwarded to the CDC's institutional review board and to the FDA.

RESULTS

Open enrollment into the Program was initiated on 20 December 2001 and was terminated on 11 February 2002. As of the termination date, a total of 5420 persons had received standardized education and 1727 persons (32%) had enrolled. Of these enrollees, 1528 (88%) opted to receive only the 40-day supply of antibiotic therapy (71% received doxycycline, 17% received ciprofloxacin, and 12% received amoxicillin) and 199 enrollees (12%) opted to receive the 40-day supply of antibiotic therapy (55% received doxycycline, 36% received ciprofloxacin, 8% received amoxicillin, and 1% received a different antibiotic) plus 3 doses of AVA. These numbers are based on data collected at enrollment. Given the nature of this public health response, it is difficult to estimate the degree of adherence or the number of participants who completed their antibiotic regimen. At the 2-month postenrollment interval, 1302 participants (75%) were

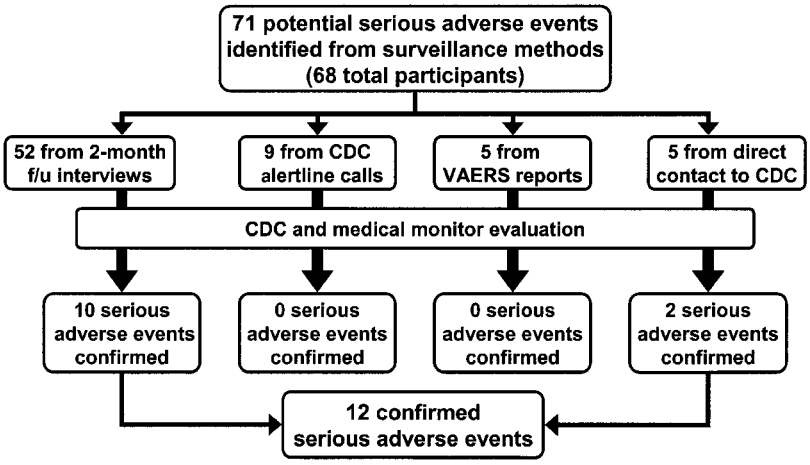


Figure 2. Sources of serious adverse events reported in the Anthrax Vaccine and Antibiotics Availability Program, December 2001–September 2002. CDC, Centers for Disease Control and Prevention; f/u, follow-up; VAERS, Vaccine Adverse Event Reporting System.

contacted by phone, and 1113 (64%) responded to a series of health status and safety-related questions (figure 1). Overall, 35 (2%) of the participants were not contacted at the 2-month follow-up because they either voluntarily withdrew from the Program earlier or could not be reached because of inadequate or invalid contact information. An additional 390 participants (23%) could not be reached by telephone, despite multiple attempts to do so at various times of the day.

Initial review of all AE reports from the 1727 enrollees identified 71 reports of potential SAEs that involved 68 different participants. Figure 2 illustrates the distribution of these potential SAEs by each surveillance method. Active surveillance, using the 2-month follow-up telephone interview, identified 52 potential SAEs, and passive surveillance, which included 3 different methods, identified another 19 potential SAEs. Further evaluation by the clinical program manager and medical monitor found that the AEs experienced by 12 of the 68 participants met the definition of an SAE (table 1). Analysis was ongoing at the time of this writing with respect to the 59 AEs evaluated as potential SAEs and to the other nonserious AEs that were identified. Although potential SAEs were identified by 4 different surveillance methods, only those detected during the 2-month follow-up interviews (10 cases) and those reported by participants who contacted the CDC directly (2 cases) comprised the AEs that met FDA criteria for an SAE. These 12 SAEs were further classified on the basis of causality assessments as definite ($n = 0$), probable ($n = 1$), possible ($n = 2$), unlikely ($n = 5$), not related ($n = 4$), or unclassifiable ($n = 0$). From reports received at the CDC through 30 September 2002, between 0.7% (12 of 1727) and 1.1% (12 of 1113) of participants experienced an SAE, regardless of its relationship to the Program. Between 0.17% (3 of 1727) and 0.27% (3 of 1113) of participants experienced an SAE that had a causal relationship to the Program that was classified as possible or probable.

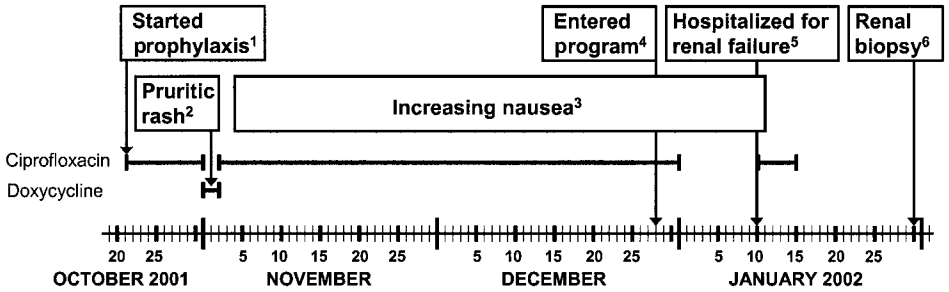
DISCUSSION

This Program, which was a part of the emergency public heath response to the first documented bioterrorism-associated anthrax attack, provided the first opportunity to evaluate SAEs associated with antimicrobial prophylaxis for up to 100 days, with or without postexposure use of AVA in a 3-dose regimen. Data collected thus far indicate that the rate of reported SAEs is low. There have been no reported deaths, and only 1 participant, who received antibiotic therapy only, was identified with a SAE classified as probably related to participation in the Program. Two participants, both of whom received antibiotic therapy only, reported having SAEs that were classified as possibly associated with program participation. The remaining participants reported SAEs that were classified as either unrelated

Table 1. Characteristics of 12 participants with serious adverse events in the Anthrax Vaccine and Antibiotics Availability Program from December 2001 through September 2002.

Case	Participant age, years	Sex	Prophylaxis received	Primary complaint(s)	Causality assessment	Date on which the clinical program manager was notified
1	44	F	Ciprofloxacin	Nausea, allergic interstitial nephritis	Probable	24 Jan
2	56	F	Doxycycline	Abdominal pain, extended work absence	Possible	30 Jan
3	46	M	Doxycycline	Liver problems	Not related	26 Feb
4	40	M	Doxycycline	Depression, extended work absence	Not related	27 Feb
5	59	F	Doxycycline	Fatigue, malaise, hypertension, extended work absence	Unlikely	2 Mar
6	49	M	Doxycycline	Allergic reaction to ciprofloxacin	Not related	4 Mar
7	58	F	Doxycycline	Bowel obstruction	Not related	22 Mar
8	41	M	Amoxicillin	Chronic sporadic diarrhea, extended work absence	Unlikely	1 Apr
9	46	M	Doxycycline	Nausea, back pain, anxiety, extended work absence	Unlikely	1 Apr
10	50	F	Amoxicillin[a]	Vomiting, rectal-vaginal prolapse	Unlikely	4 Apr
11	42	M	Amoxicillin[a]	New-onset type II diabetes mellitus, extended work absence	Unlikely	1 May
12	53	F	Doxycycline	Diarrhea, chest pain	Possible	20 May

[a] Participant also received anthrax vaccine.



1. Began 10-day course of ciprofloxacin (500-mg b.i.d) for anthrax antimicrobial prophylaxis.
2. Changed to doxycycline(100-mg b.i.d) for remaining 50 days but developed pruritic rash 2 days later. Recommenced on ciprofloxacin.
3. Participant often took ciprofloxacin only once per day as nausea worsened.
4. Received additional 40-day supply of ciprofloxacin. Discontinued medication after 3 days due to continued nausea.
5. Went to emergency department for continued severe nausea. Admission diagnosis of acute renal failure. Received ciprofloxacin 500-mg q.d. while in the hospital.
6. Renal biopsy showed allergic interstitial nephritis consistent with ciprofloxacin nephrotoxicity and hypertensive nephrosclerosis.

Figure 3. Timeline of the serious adverse event for a participant (case 1) from the Anthrax Vaccine and Antibiotics Availability Program

or unlikely to be associated with participation in the Program; this group included the 2 participants who received post-exposure AVA.

Of the 5420 people educated about the Program, 1727 (32%) elected to participate; this was a lower number of participants than had been expected. Factors that may have resulted in a relatively low participation rate included personal perception of risk, whether the program began during or after the completion of initial antibiotic prophylaxis, willingness to comply with specific informed consent requirements associated with investigational new drugs, and level of encouragement for participation received from supervisors and management across subgroups.

Of 1727 participants initially enrolled in the Program, 1113 (64%) successfully completed the 2-month follow-up interview. The interview was the most effective means of identifying both potential and confirmed SAEs (figure 2). However, additional SAEs may have gone unrecognized among the participants who either could not be contacted or declined to participate in the interviews. Because this Program was part of an emergency public health response and was not a research study, some participants lost to follow-up may have enrolled to receive prophylaxis only and were possibly less motivated to participate in the follow-up interview.

One of the FDA's criteria for an SAE was a persistent or significant disability or incapacitation. Although missed work alone was not expressly stated as part of the FDA definition of an SAE, the clinical program manager and his medical staff, working with the medical monitor, considered significant loss of work to be a possible indicator of significant disability or incapacitation. Participants missing >2 weeks of work were evaluated as having experienced a potential SAE. Six (50%) of the 12 participants with confirmed SAEs were classified as such, in part because of their extended absence from work. Only 1 SAE among these 6 was classified as possibly associated with the Program, and the remaining 5 were classified as either unlikely to be related or not related. This indicator of potential SAEs was time dependent, and active surveillance with the 2-month follow-up interview proved valuable for recognizing these potential SAEs.

The CDC received 71 notifications of potential SAEs that involved 68 participants. The CDC received 2 separate AE reports for 3 participants. Two of these 3 participants had reports that did not meet the criteria for a confirmed SAE after evaluation of the AE reports. The third participant was identified as having a confirmed SAE after receipt of a second AE report during the 2-month follow-up interview. This participant was 1 of the 6 with confirmed SAEs who was absent from work for an extended period of time.

Of the 12 participants with confirmed SAEs, 2 (17%) had received both antibiotics and AVA. This is likely a reflection of the overall distribution of participants' enrollment in the Program. The SAEs reported for the 2 participants who received AVA were each classified as unlikely to be associated with their participation in the Program. The ability to assign causality may have been limited in some cases by incomplete or inaccurate information. For each SAE, an attempt was made to contact the participant's health care provider(s) to obtain further information about the SAE, but some participants withdrew permission to contact their health care provider(s). Additionally, there were several cases in which the CDC was unable to directly contact the participant for further follow-up questioning. As a result of these limitations, a number of these causality assignments were regarded as provisional and will be reevaluated pending the availability of additional information.

Of the 9 participants determined to have an SAE that was either unrelated or unlikely to be related to the prophylaxis

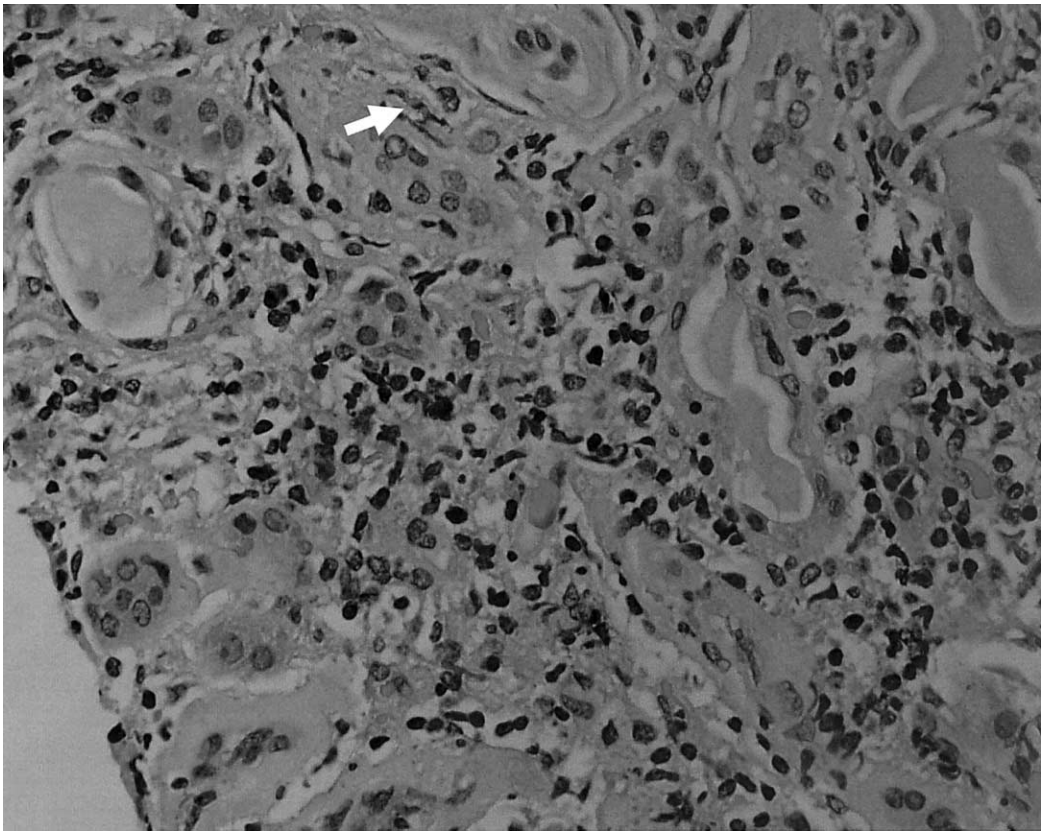


Figure 4. Renal biopsy specimen from a participant (case 1), who was identified with a serious adverse event classified as probably associated with participation in the Anthrax Vaccine and Antibiotic Availability Program, showing acute and chronic tubulointerstitial nephritis with diffuse lymphocytic infiltrate, occasional eosinophils *(arrow),* edema, basement membrane thickening, and fibrosis consistent with allergic interstitial nephritis (hematoxylin-eosin stain; original magnification, ×400).

provided in the Program, 8 had SAEs that were classified as such, in part because of symptoms or medical problems that had developed before enrollment in the Program. Seven of these 8 participants had symptoms that may have resulted in whole or in part from antimicrobial prophylaxis taken before enrollment in the Program. This supports the findings of Shepard et al. [10] in their evaluation of adherence and AEs experienced by persons receiving antimicrobial prophylaxis for an initial 60 days. Specifically, the occurrence of AEs during the first 60 days of prophylaxis did not appear to serve as a deterrent to the decision to enroll in the Program. These investigators also found that the factor most consistently associated with adherence was participation in the Program, and this was interpreted as a surrogate for the perception of individual risk.

Information on the expected occurrence of SAEs associated with antimicrobial therapy used in this Program is limited. AEs requiring discontinuation of ciprofloxacin occurred in 3.5% of participants included in clinical trials [13]. Gastrointestinal events were the most common AE reported. Pseudomembranous colitis has been reported with nearly all antimicrobial agents, including ciprofloxacin, and may range in severity from mild to life threatening. A review of AE rates among participants who received long-term (>30-day) ciprofloxacin therapy in clinical trials found an overall AE rate of 32% and a rate of gastrointestinal AEs of 22%, although no pseudomembranous colitis or previously unrecognized AE was observed [14]. Renal toxicity, including interstitial nephritis, was also reported as a rare but possible SAE associated with ciprofloxacin use, although the data consist primarily of case reports, which makes the incidence of SAEs difficult to estimate [15]. The rate of potential SAEs associated with doxycycline is also not clearly defined. In several small studies, the rate of AEs associated with doxycycline has ranged from 30% to as high as 50%, with rates of nausea and vomiting of 31% [16–19]. SAEs associated with amoxicillin have essentially been limited to sensitivity phenomena, although pseudomembranous colitis may also occur [13].

SAEs associated with AVA that were reported to VAERS were evaluated recently by the Anthrax Vaccine Expert Committee. The committee did not find a high frequency or an unusual pattern of SAEs associated with AVA [20]. A recent report from the Institute of Medicine of the National Academies (Washington, DC) that evaluated available published reports of AEs

after receipt of AVA found no evidence that SAEs, including life-threatening or permanently disabling immediate-onset AEs, occurred at higher rates among AVA recipients, compared with rates among the general population [21].

Detailed descriptions for all cases and further case discussion can be found in Appendix A, included in the online version of this article in the electronic edition of *Clinical Infectious Diseases*. Through September 2002, only 1 SAE (case 1) has been determined to be probably associated with the individual's participation in the Program (the participant received ciprofloxacin only; figure 3). After a renal biopsy was performed, this participant received a diagnosis of acute renal failure secondary to allergic interstitial nephritis and underlying chronic hypertensive nephropathy (figure 4). The SAEs of 2 participants were determined to be possibly associated with their participation in the Program.

In summary, 12 participants have been identified with an AE that satisfied the FDA criteria for an SAE. Of these, 2 SAEs were assessed as possibly and 1 as probably associated with treatment received in the Program. Follow-up of these 3 participants by the CDC was ongoing at the time of this writing. Active surveillance by direct telephone contact with participants has been the single most important tool for identifying SAEs among participants in the Program. CDC will continue to monitor the health and safety of all Program participants by active surveillance through telephone follow-up calls scheduled at 6, 12, and 24 months after enrollment. The CDC will use information collected from the Program to better refine future emergency public health responses and programs.

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An additional reference, cited only in Appendix A, appears in the electronic version of this article as item 22 in the reference list.

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